
Increased rate of miscarriage during second wave of COVID-19 pandemic in India

The lack of reliable data on the risk of miscarriage due to coronavirus disease 2019 (COVID-19) is a concern for both patients and obstetricians. A recent meta-analysis demonstrated an increased risk of adverse pregnancy outcome in low-to-middle-income countries (LMICs) when compared with high-income countries¹. The second wave of the COVID-19 pandemic was reported to be more fatal than the first wave, with increased disease severity and maternal mortality². However, the impact of the second wave of COVID-19 in India on the rate of miscarriage is unknown.

We report on the incidence of miscarriage in a cohort of pregnant and postpartum women with COVID-19 ($n=1630$) admitted to BYL Nair Charitable Hospital (NCH), Mumbai, India, between 1 April 2020 and 4 July 2021, during the first (1 April 2020 to 31 January 2021) and second (1 February 2021 to 7 July 2021) waves of the COVID-19 pandemic (Figure 1). Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed using reverse transcription polymerase chain reaction of nasopharyngeal swabs, as per the national testing guidelines. The data of the cohort admitted during the COVID-19 pandemic were compared to those of 11 952 women admitted prior to the pandemic between 1 October 2016 and 30 September 2018. This prepandemic period was selected due to uninterrupted obstetric and gynecological services and data availability. Miscarriage was defined as spontaneous pregnancy loss before 20 weeks of gestation or delivery of a dead fetus weighing less than 500 g. Intrauterine fetal demise (IUFD) was defined as *in-utero* death of a fetus that was confirmed by ultrasound before delivery. The study was approved by the ethics committees of TNMC (ECARP/2020/63) and ICMR-NIRRH (IEC no. D/ICEC/Sci-53/55/2020) and registered with the Clinical Trial Registry of India (CTRI#2020-025423).

The rate of miscarriage per 1000 births was significantly higher during the second wave of the COVID-19 pandemic than that during the first wave (82.6 *vs* 26.8; $P<0.001$) or the prepandemic period (odds ratio, 1.7 (95% CI, 1.16–2.59); $P=0.006$). The rate of miscarriage per 100 admissions during the second wave of the COVID-19 pandemic was also significantly higher than

that during the first wave ($P<0.004$) or the prepandemic period ($P=0.003$) (Table 1). During the prepandemic period, the rate of miscarriage was significantly higher in the months February to July (in 2017 and 2018) (55.7 per 1000 births) compared with the months April to January (in 2016, 2017 and 2018) (42.8 per 1000 births) ($P=0.004$). Even so, the rate of miscarriage during the second wave of the COVID-19 pandemic (February–July 2021) was significantly higher compared with the same months in the prepandemic period in 2017 and in 2018 at NCH ($P=0.044$) (Tables S1 and S2).

The rate of IUFD was significantly higher during the COVID-19 pandemic compared with that during the prepandemic period ($P=0.006$). The incidence of first- and second-trimester IUFD during the COVID-19 pandemic was higher compared with that in the prepandemic period, but the difference did not reach statistical significance ($P=0.09$). The rate of second-trimester miscarriage was significantly higher during the COVID-19 pandemic as compared to the prepandemic period ($P<0.001$) (Table 1). A higher number of symptomatic women with COVID-19 and miscarriage were reported during the first wave (7/22 (31.8%)) as compared to the second wave (5/28 (17.9%)) of the COVID-19 pandemic. During the second wave of the COVID-19 pandemic, 96.4% (27/28) of women with miscarriage conceived spontaneously, as compared to a rate of 77.3% (17/22) during the first wave ($P=0.07$).

Our study demonstrates that the risk of miscarriage during the second wave of the COVID-19 pandemic was three times higher compared with the first wave of the pandemic and two times higher compared with

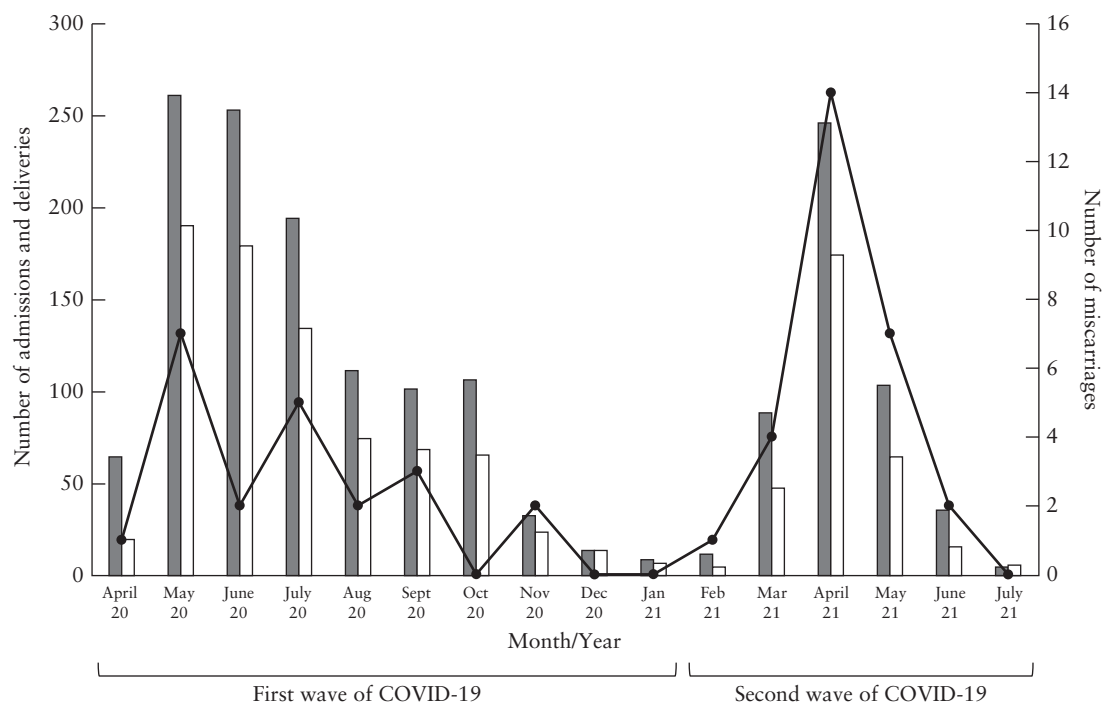


Figure 1 Numbers of pregnant and postpartum women with COVID-19 who were admitted to BYL Nair Charitable Hospital (NCH) (■), those who delivered at NCH (□) and those who had a miscarriage (—●—) during the first (1 April 2020 to 31 January 2021) and second (1 February to 7 July 2021) waves of the COVID-19 pandemic in India.

Table 1 Pregnancy outcome of women admitted* to BYL Nair Charitable Hospital in Mumbai, India, prior to the COVID-19 pandemic (1 October 2016 to 31 September 2018) and those admitted with COVID-19 during the pandemic (1 April 2020 to 4 July 2021), overall and during the first wave (1 April 2020 to 31 January 2021) vs second wave (1 February 2021 to 7 July 2021)

Outcome	Prepandemic period (n = 11 952)	Women with COVID-19 during the pandemic							
		Overall (n = 1630)	Odds ratio (95% CI)†	P‡	First wave (n = 1143)	Second wave (n = 487)	P‡	P§	P¶
Delivery of infant > 500 g	7222	1136	—	—	807	329	—	—	—
Number of births**	7361	1161	—	—	822	339	—	—	—
Miscarriage (per 100 admissions)	349 (2.9)	50 (3.1)	—	0.74	22 (1.9)	28 (5.7)	0.004	0.05	0.003
Miscarriage (per 1000 births)	349 (47.4)	50 (43.1)	0.91 (0.67–1.23)	0.53	22 (26.8)	28 (82.6)	< 0.001	0.009	0.006
First trimester	281/349 (80.5)	30/50 (60.0)	0.36 (0.19–0.69)	0.001	13/22 (59.1)	17/28 (60.7)	> 0.99	0.02	0.02
Second trimester	68/349 (19.5)	20/50 (40.0)	2.75 (1.48–5.14)		9/22 (40.9)	11/28 (39.3)			
Type of miscarriage according to US findings at admission									
IUFD	151/349 (43.3)	32/50 (64.0)	2.33 (1.26–4.31)	0.006	15/22 (68.2)	17/28 (60.7)	0.76	0.02	0.07
First trimester	105/349 (30.1)	21/50 (42.0)	1.68 (0.92–3.09)	0.09	10/22 (45.5)††	11/28 (39.3)	0.77	0.15	0.39
Second trimester	46/349 (13.2)	11/50 (22.0)	1.86 (0.89–3.88)	0.09	5/22 (22.7)‡‡	6/28 (21.4)	> 0.99	0.20	0.25
Anembryonic pregnancy	73/349 (20.9)	6/50 (12.0)	0.52 (0.21–1.26)	0.18	3/22 (13.6)	3/28 (10.7)	> 0.99	0.58	0.23
Live fetus (second-trimester miscarriage)	20/349 (5.7)	5/50 (10.0)	1.83 (0.65–5.11)	0.22	2/22 (9.1)	3/28 (10.7)§§	> 0.99	0.38	0.23
Complete/incomplete miscarriage¶¶	105/349 (30.1)	7/50 (14.0)	0.38 (0.16–0.87)	0.01	2/22 (9.1)	5/28 (17.9)	0.44	0.04	0.20

Data are given as *n* or *n/N* (%), unless indicated otherwise. Chi-square or Fisher's exact test was applied at a significance level of $P < 0.05$.



*Women were admitted for delivery, miscarriage, ectopic pregnancy and other medical complications. *P*-values are given for comparison of the following groups: †prepandemic vs pandemic; ‡first wave vs second wave; §prepandemic vs first wave; ¶prepandemic vs second wave.

**There were 23 twin births and one triplet birth among deliveries during the COVID-19 pandemic and 135 twin births and two triplet births during the prepandemic period. ††One intrauterine fetal death (IUFD) case at 11 weeks had active tuberculosis. ‡‡One case of IUFD at 24 weeks had plasmodium vivax malaria. §§One miscarriage case had neurological complication related to COVID-19 (Guillain-Barré syndrome) and autoimmune syndrome. ¶¶No data on viability or IUFD were available. Complete miscarriage was defined as previously confirmed pregnancy and no product of conception detected on ultrasound (US) at admission. Incomplete miscarriage was defined as remnants of products of conception detected on US at admission.

the prepandemic period. Although seasonal variation was observed and the rate of miscarriage was higher during February–July compared to April–January in the prepandemic period, we observed a significantly higher rate of miscarriage during the same months in the second wave of the COVID-19 pandemic. This is the first study to report on the increased rate of miscarriage during the second wave of the COVID-19 pandemic in India. The observed increased risk of miscarriage in women with COVID-19 supports the findings of a study conducted in Turkey³ but is in contrast to the findings of the studies from the USA⁴ and Canada⁵. The findings of our study support the observations that COVID-19 could disproportionately affect pregnant women in LMICs¹ and women from an Asian ethnic background. The increased miscarriage rate during the second wave of the pandemic could be due to the high infectivity and virulence of the Delta (B.1.617.2) variant of SARS-CoV-2, which was reported to be responsible for the second wave in India⁶, leading to more IUFDs in both trimesters. Higher COVID-19 rates, fewer antenatal care visits, reduced access to nutritious food and travel restrictions during the second wave could also account for the increased rate of miscarriage during the second wave of the pandemic. However, further studies are required to demonstrate the causal link between fetal death and COVID-19.

Limitations of this study include the lack of SARS-CoV-2 testing of products of conception and data on genome sequencing of SARS-CoV-2 strains.

In conclusion, our study provides evidence to support counseling of women wishing to become pregnant during the ongoing COVID-19 pandemic and of those who become infected during the first trimester of pregnancy. In our study, COVID-19 appeared to be associated with an increased risk of miscarriage, especially during the second wave of the pandemic. Our findings are important for public health policy, especially for prioritizing the vaccination of pregnant women in India and other LMICs in light of the predicted third wave of the COVID-19 pandemic.

R. K. Gajbhiye^{1#} , A. Tilve^{2#}, S. Kesarwani²,
S. Srivastava², S. J. Kore², K. Patil², S. D. Mahale¹
and N. N. Mahajan^{2*} 

¹ICMR-National Institute for Research in Reproductive Health, Mumbai, India;

²Department of Obstetrics and Gynecology, Topiwala National Medical College & BYL Nair Charitable Hospital, Mumbai, India

*Correspondence.

(e-mail: nirajdr@hotmail.com)

DOI: 10.1002/uog.24784

#R.K.G. and A.T. contributed equally to this study.

Acknowledgments

We thank Dr Periyasamy Kuppusamy for his assistance in statistical analysis. The study was funded by intramural grant of ICMR-NIRRH (No. ICMR-NIRRH/RA/

1070/05-2021). R.K.G. is an awardee of the DBT Wellcome Trust India Alliance Clinical and Public Health Intermediate Fellowship (Grant no. IA/CPHI/18/1/503933).

References

1. Gajbhiye RK, Sawant MS, Kuppusamy P, Surve S, Pasi A, Prusty RK, Mahale SD, Modi DN. Differential impact of COVID-19 in pregnant women from high-income countries and low- to middle-income countries: A systematic review and meta-analysis. *Int J Gynaecol Obstet* 2021; 55: 48–56.
2. Mahajan NN, Pophalkar M, Patil S, Yewale B, Chaaithanya IK, Mahale SD, Gajbhiye RK. Pregnancy Outcomes and Maternal Complications During the Second Wave of Coronavirus Disease 2019 (COVID-19) in India. *Obstet Gynecol* 2021; 138: 660–662.
3. Sacinti KG, Kalafat E, Sukur YE, Koc A. Increased incidence of first-trimester miscarriage during the COVID-19 pandemic. *Ultrasound Obstet Gynecol* 2021; 57: 1013–1014.
4. Jacoby VL, Murtha A, Afshar Y, Gaw S, Asiodu I, Tolosa J, Norton ME, Boscardin J, Flaherman V. Risk of Pregnancy Loss Prior to 20 weeks Gestation with COVID-19. *Am J Obstet Gynecol* 2021; 225: 456–457.
5. Rotshenker-Olshinka K, Volodarsky-Perel A, Steiner N, Rubinfeld E, Dahan MH. COVID-19 pandemic effect on early pregnancy: are miscarriage rates altered, in asymptomatic women? *Arch Gynecol Obstet* 2021; 303: 839–845.
6. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, Rakshit P, Singh S, Abraham P, Panda S, Team N. SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. *Microorganisms* 2021; 9: 1542.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Seasonal variation in the rate of miscarriage observed prior to *vs* during the COVID-19 pandemic

Table S2 Number of births and miscarriages in the evaluated period prior to the COVID-19 pandemic (1 October 2016 to 31 September 2018), overall and according to month